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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/774,092	02/06/2004	Ernesto A. Brovelli	AM1150	7125

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IN RE: 28533
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EXAMINER	
LEITH, PATRICIA A	

ART UNIT	PAPER NUMBER
1655	

MAIL DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/774,092	BROVELLI ET AL.	
	Examiner	Art Unit	
	Patricia Leith	1655	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *4/10/2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *3,5-7 and 23-25* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) _____ is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *3,5-7 and 23-25* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 4/10/2008 has been entered.

Claims 3, 5-7 and 23-25 are pending in the application and were examined on their merits.

The previous rejection of claims 3, 5-7 and 23-25 under 35 USC 112 First paragraph for lacking written description is herein removed due to Applicants' amendments to claims 3 and 24. However, a new rejection under 35 USC 112 First paragraph is in order due to Applicants' amendments.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 3, 5-7 and 23-25 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicants have amended claims 3 and 24 to recite:

"(i) a standardized concentration of the marker compound that is used to prepare an extract…". This phrase is considered New matter because there is nowhere in the specification which teaches that the maturation stage *is selected* with a standardized concentration of the marker compound. The Instant specification teaches that chicoric acid levels were measured from plants in various maturation stages, however, that the levels of chicoric acid were relatively similar. The natural content of the chicoric acid is not considered 'standardization'; rather, standardization is what occurs after the extract is collected; it is a means for manipulating the extract to contain certain levels of a compound. Further, Applicant has not pointed out in the specification that the concentrations of chicoric acid would be considered to be 'standardized.'

In order to overcome this rejection; Applicant is asked to either delete the New Matter in the claim, or to point out specifically where this information can be found.

Because claims 5-7, 23 and 25 depend upon either claims 3 or 24 respectively, claims 5-7, 23 and25 necessarily contain all of the limitations of either claims 3 or 24 respectively and therefore also contain New Matter and are appropriately rejected under this statute.

Claim Rejections - 35 USC § 103

Claims 3, 5-7 and 24 are newly rejected under 35 U.S.C. 103(a) as being unpatentable over A in view of C in view of E or B in view of C in view of E; wherein A = Seidler – Lozykowska et al. (2003), B= Dou et al. (2001 – Abstract), C= Rininger et al. (2000) and E= Gahler et al. (US 6,511,683). Seidler – Lozykowska et al. may be referred to as "SL et al."

The teachings of A, B and C were keenly discussed in previous Office actions.

This new rejection is being placed in the event that Applicants specifically amend claim 3 or 25 to include specifically that the marker compound is chicoric acid for example. Further, the Gahler et al. reference is particularly pertinent to the claimed

invention in that Gahler et al. recognize the need and advantages of standardizing Echinacea extracts for several markers to afford an extract with optimized medicinal potential. Gahler et al. further clearly recognize that Echinacea must be harvested at various times in order to obtain plants with desired amounts of analyte marker compounds:

Gahler et al. . (US 6,511,683) recognized the advantage of standardizing extracts of Echinacea for several desired endogenous compounds such as chicoric acid, alkylamides and polysaccharides (see entire patent and Abstract):

> [I]t is desirable to formulate Echinacea compositions to contain standardized amounts of biologically active components derived from Echinacea plants. Such standardized, Echinacea compositions provide the consumer with a consistent, effective dose of one or more, biologically active, Echinacea components. In particular, there is a strong commercial market for Echinacea extracts containing a high concentration of one or more, biologically active, Echinacea components believed to promote good health. Such highly enriched extracts can be used directly as dietary supplements, or can be blended with other Echinacea extracts to prepare dietary supplements containing standardized amounts of biologically active, Echinacea components. (col. 1, lines 23-37)

Gahler et al. clearly established the desirability of standardizing Echinacea for several markers in order to produce extracts with added medicinal benefit (see column 1):

> Scientific studies indicate that Echinacea-derived polysaccharides, alkylamides and chicoric acid (a caffeic acid derivative also known as chicoric acid, 2,3-o-di-caffeoyl-tartaric acid) each possess health-promoting properties. For example, alkylamides from Echinacea have been shown to stimulate phagocytosis in mice granulocytes at concentrations of about 0.1 parts per million (ppm). Bauer, R. et al., Arzneim.-Forsch./Drug Research, 38: 276-281 (1988). Similarly, chicoric acid has been shown to increase

> phagocytosis in granulocytes, and may stimulate the immune system at concentrations as low as 0.01 ppm. See e.g., A. Awang et al., supra. Echinacea polysaccharides have been shown to inhibit hyaluronidase, increase phagocytosis, induce the release of interferon-6, and enhance resistance to C. albicans infection in mice. See, e.g., A. Awang et al., supra; Wagner, H, et al. Arzneim.-Forsch./Drug Research, 35: 1069-1075 (1985).
>
> (7) Numerous factors must be considered and optimized in order to produce Echinacea extracts having a high concentration of polysaccharides, alkylamides and/or chicoric acid. For example, the amounts of polysaccharides, alkylamides and chicoric acid in Echinacea plants are influenced by the species of the plant, the age of the plant and the plant growth conditions. Additionally, the solvents and process parameters, such as temperature and length of extraction period, utilized to extract polysaccharides, alkylamides and chicoric acid from Echinacea plants can greatly affect the yield of these components.
>
> (8) Thus, there is a need for methods for efficiently extracting polysaccharides, alkylamides and chicoric acid from Echinacea plants, and for Echinacea extracts containing a high concentration of polysaccharides, alkylamides and/or chicoric acid. Further, there is a need for standardized Echinacea compositions containing a predetermined, desired amount of Echinacea extracts, including polysaccharide, alkylamide and/or chicoric acid extracts.

Gahler et al. additionally recognize the importance of selecting an Echinacea plant at a particular growth stage with the desired amounts of each analyte marker compound (see col. 2, and columns 11-12 for example). Here, Gahler et al. provides detailed information of how to select Echinacea for optimum analyte concentration.

Gahler et al. clearly established that their extracts containing multiple marker compounds influenced immune system parameters such as IL-2 and TNF-α (inter alia) (see, for example, Figures 1-7 and 'Brief Description of the Drawings').

Claims 3, 5-7 and 23-25 are newly rejected under 35 U.S.C. 103(a) as being unpatentable over A in view of C in view of D in view of E or B in view of C in view of D in view of E; wherein A = Seidler – Lozykowska et al. (2003), B= Dou et al. (2001 – Abstract), C= Rininger et al. (2000) D= Wyllie et al. (US 2003/0235890) and E= Gahler et al. (US 6,511,683). Seidler – Lozykowska et al. may be referred to as SL et al. It is noted that the Wyllie et al. reference was originally placed in the Office action of 12/14/2006; however, was inadvertently omitted from subsequent Office actions.

The teachings of A, B and C were discussed in previous Office actions as well as supra. A, B and C did not specifically teach the use of THP-01 cells as indicated by claims 23 and 25.

(D), Wyllie et al. (US 2003/0235890) teach that RAW cells as well as THP-1 cells were both known for being immunopotentiating models (see [0306] for example).

One of ordinary skill in the art would have been motivated to substitute THP-1 cells for the RAW cells of Rininger et al. because THP-1 cells would have been a better model for human in-vivo immunopotentiating ability of Echinacea products.

Further, Applicant has not indicated, nor is there any data present which would indicate that the use of THP-1 cells would provide for any additional/unexpected benefit over RAW 264.7 cells. Each THP-1 (human) and RAW 264.7 (murine) are both

macrophage/monocyte cells which express cytokines such as TGF a and Interleukins and both are known in the art to be used in-vitro to assess immunopotentiating activity of analyte compounds. Therefore one of ordinary skill in the art would have a reasonable expectation that either cell would be suitable for quantitating immunopotentiating activity.

The teachings of E (Gahler et al.) were discussed above. This new reference is being placed in the event that Applicants specifically amend claim 3 or 25 to include specifically that the marker compound is chlorogenic acid. Further, the Gahler et al. reference is particularly pertinent to the claimed invention in that Gahler et al. recognize the need and advantages of standardizing Echinacea extracts for several markers to afford an extract with optimized medicinal potential. Gahler et al. further clearly recognize that Echinacea must be harvested at various times in order to obtain plants with desired amounts of analyte marker compounds:

Response to Arguments

Applicants' arguments were fully considered, but not found persuasive.

Applicants argue:

> …according to Section 2141 of the MPEP, when applying 35 U.S.C. 103, the following tenants of patent law must be adhered to: (A) The claimed invention must be considered as a whole; (B) the references must be considered as a whole and must suggest the desirability and thus the obviousness of making the combination; (C) the references must be viewed without the benefit of impermissible hindsight…; and (D) reasonable expectation of success is the standard with which obviousness is determined. Hodosh v. Block Drug Co., Inc…Applicants thus comment that "Under these standards, the claims are not obvious in view of the cited references. First the claimed invention as a whole is a method for determining optimal harvest window of Echinacea, based on selecting a plant maturation stage that has both a concentration of a marker compound that is greater than zero and acceptable for preparing a standardized extract, and immonostimulatory activity. the claimed method also includes a step of preparing a standardized extract at that selected maturation stage. (p. 8, Remarks).

It is noted that the Examiner has based her rejections upon the 'Graham inquiries; that is:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Based upon these factors, it is determined that the claimed invention as a whole is obvious in view of the combination of the cited prior art references for reasons keenly pointed out in previous Office actions, as well as herein.

It is noted that the prior art does not specifically teach all of the claim limitations in one reference, hence, there is no 102 rejection. However, the invention as a whole is rendered obvious by the prior art references. Echinacea plants were well-known in the art at the time the invention was made and exhaustively studied for their medicinal

effects. The claimed invention as a whole is obvious, and there is no individual step in any of the method claims which was not already known or made obvious by the prior art. That is, there is no novel step or idea in the method claims which makes it unobvious over the prior art references. According to the prior art references, as keenly pointed out in the previous Office action, Echinacea plants were known to be studied at different maturation stages for marker compounds to select for optimum levels of compounds. Echinacea plants were also known to contain immunopotentiating activity, and the activities were known to be studied and already determined to depend, in part, upon the harvesting time of the Echinacea. Additionally, Applicants' method for determining the level of immunopotentiating activity, as well as marker immuno stimulatory products were known in the art at the time the invention was made. While no one, individual reference taught all of these steps together; the ordinary artisan would have been motivated to perform the claimed method in order to optimize medicinal efficacy of an Echinacea extract and standardization would have been routine in manufacturing extracts with essentially uniform chemical constituents and hence, medicinal effectiveness: ***"[a] person of ordinary skill is also a person of ordinary creativity, not an automaton*** *KSR* 127S. Ct. at 1742 (emphasis added).

Applicants argue that:

> Specifically, two of the cited references, Seidler-Lozykowska and Dou, examine when the greatest levels of typical marker compounds…used to standardize extracts may be obtained and from which specific parts of the plant may be obtained….neither Seidler-Lozykowska nor Dou

> discuss any immunopotentiating activity of Echinacea…Rininger teaches that standardized Echinacea extracts do not exhibit immunostimulatory activity. (p. 9, Remarks).

The desirability of creating Echinacea extracts with increased immunopotentating activity, as well as increased levels of compounds such as chicoric acid was *well-documented in the art* (see cited references, especially Gahler et al.). It is deemed that the method claims of the Instant invention would have been well-within the purview of the ordinary artisan at the time the invention was made having the above-cited references before him or her. One of ordinary skill in the art would have had a reasonable expectation of success in choosing an Echinacea plant with 'the highest' amount of immuno-stimulatory' activity and at least some amount of chicoric acid because both immuno-stimulatory activity as well as chicoric acid were desired at the time the invention was made.

While Applicants argue that Rininger teaches that standardized extracts are "inactive" for immunostimulatory activity (p. 9, Remarks). Again, it is noted that Applicants point to one embodiment of Rininger which discusses a single standardized extract containing 4% phenolic standardized extract did not induce macrophage stimulation. This does not indicate that <u>all extracts</u> from Echinacea standardized for chicoric acid will be inactive for immunopotentiating activity. Furthermore, Rininger explicitly teaches that polysaccharides from Echinacea do have immunopotentiating activity; *polysaccharides being one of the marker compounds specifically claimed by Applicants.* Therefore, Applicants' arguments pertaining to the allegation that Rininger

did not teach compounds with immunopotentiating activity is without merit; clearly, a majority of their reference is directed toward macrophage stimulation with endogenous Echinacea compounds.

In either respect, it is deemed that it would have been obvious to select for a marker compound such as polysaccharides or chicoric acid because these marker compounds were known to have medicinal activity and hence were desirable. One of ordinary skill in the art would clearly understand that selection of Echinacea with regard to polysaccharide content for example, would have an immunopotentiating effect. It appears that Applicants are attempting to extrapolate the teachings of Rininger which state that a standardized extract containing 4% phenolics to *any* standardized extract, which is improper. This is especially in view of Gahler et al. who reported that Echinacea extracts containing Chicoric acid possessed immune potentiating activity (see, *Id*). . *Furthermore, Rininger* ***explicitly*** *teaches that polysaccharides from Echinacea* ***do have*** *immunopotentiating activity; polysaccharides* ***being one of the marker compounds specifically claimed by Applicants***. Further, the immunopotentiating activity of the standardized extracts analyzed by Rininger were of commercial Echinacea preparations (e.g., standardized for 4% phenolics). These standardized extracts were standardized for phenolics and not for immunopotentiating compounds. The ordinary artisan would have easily recognized that because compounds such as polysaccharides were known and proven to have immunopotentiating activity, that standardization of these compounds would have

clearly been advantageous, this is especially in view of Gahler et al.; said patent discussing the advantageous nature of standardization of Echinacea extracts for multiple compounds including chicoric acid as well as polysaccharides for additive medicinal benefit.

It must be reiterated again that Applicant's claims are not limited to wherein the marker compounds are phenolic compounds; rather, Applicants' claims are directed toward either any marker compound as in the broadest claims, or limited to marker compounds such as chicoric acid, alkylamides, glycoproteins and polysaccharides as indicted in claim 5. Further, the inclusion of the Gahler et al. patent obviates these arguments because Gahler et al. clearly teach the advantageous nature of selecting harvested Echinacea plants with regard to levels of multiple markers such as chicoric acid as well as polysaccharides.

Applicants argue:

> Thus, at a minimum, one of ordinary skill in the art may would conclude from these teachings of Rininger -- that Echinacea extracts standardized to 4% phenolic acids are not immunostimulatory, that marker compounds commonly used to standardize Echinacea extracts do not provide any immunostimulatory activity to an Echinacea extract, and that non-standardized Echinacea extracts do exhibit immunostimulatory activity -- that standardized Echinacea extracts do not necessarily or always exhibit immunopotentiating activity and may not exhibit any such activity.

However, again, the claims may be specifically directed toward wherein the marker compound is a polysaccharide and therefore, the teachings of Rininger which

demonstrate that a randomly chosen extract of Echinacea which was standardized for 4% phenolics is not quite pertinent to the scope of the claimed invention which may be specifically directed toward wherein the marker compound is a polysaccharide and thus, it is not accepted that Rininger 'teaches away' (Appilcants' arguments p. 10, Remarks) from the use of a standardized extract which possesses immunostimulatory activity. This is especially true in view of Gahler et al. who clearly teach that standardization of Echinacea extracts including several analyte compounds such as phenolics in combination with polysaccharides are advantageous for providing optimum medicinal qualities.

Applicants argue that "[t]he greatest concentration of a marker compound does not necessarily correspond to the highest level of immune-stimulatory product. Claims 3 and 24, which provide a method for determining the optimal harvest window…requires a concentration of marker compound for preparing a standardized extract…having a highest level of immune-stimulatory product" (p. 11, Remarks). However, again, these claims can be directed toward wherein the marker compound is polysaccharide. Further, In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

The Supreme court has acknowledged that:

> When a work is available in one field of endeavor, design incentives and other market forces can prompt variations of it, either in the same field or a different one. **If a person of ordinary skill can implement a predictable varition..103 likely bars its patentability**…if a technique has been used to improve one device, and a person of ordinary skill in the art would recognize that it would improve similar devices in the same way, using the technique is obvious unless its actual application is beyond that person's skill. A court must ask whether the improvement is more than the predictable use of prior-art elements according to their established functions…
>
> …the combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results (see *KSR International Co. v. Teleflex Inc*., 82 USPQ2d 1385 U.S. 2007) emphasis added.

[If]… there are [a] finite number of identified, predictable solutions, [a] person of ordinary skill in art has good reason to pursue known options within his or her technical grasp, and if this leads to anticipated success, it is likely product of ordinary skill and common sense, not innovation *KSR International Co. v. Teleflex Inc*., 82 USPQ2d 1385 U.S. 2007.From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Patricia Leith whose telephone number is (571) 272-0968. The examiner can normally be reached on Monday - Friday 8:30am-5:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Terry McKelvey can be reached on (571) 272-0775. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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